UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,734	05/27/2005	Joseph Itskovitz-Eldor	29601	3958

67801 7590 10/20/2009

MARTIN D. MOYNIHAN d/b/a PRTSI, INC.
P.O. BOX 16446
ARLINGTON, VA 22215

EXAMINER	
KIM, TAEYOON	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
10/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,734	ITSKOVITZ-ELDOR ET AL.	
	Examiner	Art Unit	
	TAEYOON KIM	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *193-202,205 and 214-234* is/are pending in the application.

4a) Of the above claim(s) *194,201 and 216-234* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *193,195-200,202,205,214 and 215* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/2/09, 7/18/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 6/10/2009 has been received and entered into the case.

Claims 194, 201 and 216-234 have been withdrawn from consideration as being drawn to non-elected subject matter, claims 1-192, 203, 204 and 206-213 have been canceled, and claims 193, 195-200, 202, 205, 214 and 215 have been considered on the merits. All arguments have been fully considered.

Response to Arguments

Applicant's arguments filed 6/10/2009 have been fully considered but they are not persuasive.

In the response, applicant alleged that Lumelsky et al. in view of Dang et al. do not teach or suggest culturing dissociated cells leading to the formation of surface bound clusters.

The dissociating EBs formed in the method of Lumelsky et al. is obvious to a person of ordinary skill in the art since the method of Lumelsky et al. is intended to select pancreatic endocrine precursor cells from embryoid bodies (EB) generated from a culture of undifferentiated ES cells (par. 10, 97). Thus, a person of ordinary skill in the art would certainly recognize that the selection step of Lumelsky et al. can be carried out by isolation of the desired cells by dissociation of the EB. Dang et al. teach one of well known methods for selecting cells with a specific phenotype by using flow cytometry, and thus, the selection of pancreatic endocrine stem or progenitor cells can be carried out by the method of Dang et al.

Applicant alleged that Lumelsky et al. with Dang et al. would end up with a dissociated cell culture incapable of forming clusters. This argument is merely the argument of counsel and

is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

While Lumelsky et al. do not particularly teach to plate dissociated EB cells on the adherent culture plates, Lumelsky et al. teach to plate EB cells onto a surface that permits adhesion of pancreatic endocrine stem cells or precursor cells (par. 98).

First, it would have been obvious to a person of ordinary skill in the art to dissociate EBs for further selection of desired cell population since it is extremely well known that EBs contain various different cell populations destined for different lineages. Since Lumelsky et al. utilize adherent culture condition in serum-free medium for selection of pancreatic endocrine stem or progenitor cells, it would have been obvious to a person of ordinary skill in the art to dissociate the EBs to identify and isolate pancreatic endocrine stem or progenitor cells. In fact, In the review article by Donovan et al. (Nature, 2001), the EBs grown in suspension culture can be plated to yield differentiating cells upon dissociation (see Fig. 2, p.93).

In another embodiment, Lumelsky et al. also teach the isolation of pancreatic endocrine stem or progenitor/precursor cells by specific markers including nestin, PDX-1, insulin, glucagon, somatostatin, etc. (par. 100). Based on the identification step using pancreatic endocrine stem or progenitor cell specific markers (nestin, PDX-1, insulin, etc.), it would have

been obvious to a person of ordinary skill in the art first to carry out a dissociation step of the EBs into single cells, and perform flow cytometry based on their expression markers (nestin, PDX-1, insulin, etc.) to isolate the desired cell population. A person of ordinary skill in the art would recognize that the method of Dang et al. including dissociating the EBs followed by flow cytometry using the markers would be a predictable solution for the selection method of Lumelsky et al., and then plating the selected cells onto the surface for adherent culture, followed by expansion of isolated pancreatic stem cells.

While Lumelsky et al. do not particularly disclose that the adherent culture would result in the formation of the cluster, since the method steps of Lumelsky et al. are considered the same, and thus, the results obtainable from the method should be the same. Therefore, it is considered that the pancreatic endocrine stem or progenitor cells obtained by the method of Lumelsky et al. inherently form clusters under the condition of adherent culture taught by Lumelsky et al.

With regard to the limitation of "inhibiting growth of non-insulin producing cells", applicant alleged that the references do not teach the limitation. It is acknowledged that the cited references do not particularly disclose the limitation, however, as Lumelsky et al. teach the use of serum-free media for the culturing selected pancreatic stem or progenitor cells, and this is the same condition disclosed by the current specification (p.11, lines 6-12), therefore, the culture condition of Lumelsky et al. inherently carry out the intended result of inhibiting growth of non insulin producing cells.

Applicant asserted that the review article by Kania et al. renders the claim rejection moot because none of studies discussed by Kania et al. described or suggested use of the cell

dissociation, cluster-culturing step of the present invention. This argument is not persuasive per the discussion above based on the inherent effect of culturing pancreatic endocrine stem or progenitor cells selected from EBs by dissociation and culturing them under the adherent culture would result in the formation of clusters of the cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 193, 195-200, 202, 205, 214 and 215 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lumelsky et al. (of record) in view of Dang et al. (of record) in further view of Ling et al. (of record).

Lumelsky et al. teach a method of producing pancreatic endocrine cells by generating embryoid bodies from ES cells in suspension culture (e.g. culturing cells on non-adherent bacterial culture dishes) (see paragraphs [0093]-[0096]), selecting nestin-positive pancreatic endocrine stem cells (a pancreatic islet cell progenitor) by culturing the cells of embryoid bodies (EBs) on substrate-coated surface (thus forming surface bound cell clusters) (see paragraphs [0096]-[0099]). The pancreatic endocrine stem cells are expanded and differentiated into mature endocrine cells which produce and secrete insulin (see paragraphs [0101]-[0114]).

Although Lumelsky et al. teach isolation of pancreatic precursor cells from EB, it does not particularly teach a step of dissociating EB into single cells displaying at least one characteristic associated with a pancreatic islet phenotype.

Dang et al. teach dissociation of EB into single cells for the subsequent analysis by flow cytometry (p. 444, right col. 2nd para.).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to dissociate EB of Lumelsky et al. to obtain single cells and isolate cells having pancreatic progenitor phenotype (nestin-positive) by flow cytometry as taught by Dang et al.

Since Lumelsky et al. teach isolation of pancreatic progenitor cells from EB based on the expression of nestin or other specific marker expression (PDX-1, insulin, etc. par. 100), and it is well known in the art that nestin positive cells from EB can be identified by flow cytometry, which requires dissociation into single cells, a person of ordinary skill in the art would have been motivated to try the dissociation technique of Dang et al. to obtain dissociated EB for identification of nestin-positive pancreatic progenitor cells.

The Supreme Court recently states in KSR v. Teleflex (550 US82 USPQ2d 1385, 2007) "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." See also M.P.E.P. §2141.

Although Lumelsky et al. do not particularly teach a culturing condition suitable for formation of surface bound cell clusters and inhibiting growth of non insulin producing cells, since Lumelsky et al. utilize serum free media such as ITSF for the culture of pancreatic precursor cells and these cells are plated onto a surface that permits adhesion of pancreatic endocrine stem or progenitor cells (para. 98 and 99), the method of Lumelsky et al. inherently promote formation of surface bound cell clusters and inhibiting growth of non-insulin producing cells as claimed in the current invention.

Lumelsky et al. do not teach a step of maintaining insulin producing cells for at least 14 days in a suspended culture.

Ling et al. teach a culture condition for islet β-cells which comprises single cell suspension culture of β cells in serum-free medium supplemented with 10 mM glucose (see Abstract, and Materials and Methods).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use the culture condition of Ling et al. to maintain insulin producing cells of Lumelsky et al.

The skilled artisan would have been motivated to make such a modification because the insulin producing cells obtainable from the ES cells of Lumelsky et al. would be similar, if not identical, to β-cells of Ling et al. Therefore, a person of ordinary skill in the art would recognize the culture condition of Ling et al. suitable for the insulin secreting/producing cells of Lumelsky et al., and a person of ordinary skill in the art would have reasonable expectation of success in maintaining the insulin producing cells of Lumelsky et al. with serum free medium containing 10 mM glucose.

M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

With regard to the limitation of "at least 14 days" in claim 196, although Ling et al. discloses only 9 days in culture, however, the examiner takes the position that the culture condition of Ling et al. would be sufficient to preserve insulin producing cells of Lumelsky et al. at least 14 days. This is because the culture condition suitable for at least 14 days of maintaining insulin producing cells claimed in the current application is identical to the culture condition of Ling et al. used for maintaining the pancreatic endocrine cells of Lumelsky et al.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' culture condition differs, and if so to what extent, from the culture condition discussed in Ling et al. Accordingly, it has been established that the prior art culture condition demonstrates a reasonable probability that it is either identical or sufficiently similar to the claimed culture condition that whatever differences exist are not patentably

significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

With the limitation of claim 198, Lumelsky et al. teach insulin cell cluster suspension (para. 171). Furthermore, since the culture condition of Ling et al. discloses that single cell suspension culture of beta cells would eventually form aggregates (see Materials and Methods in p.2614, right column and p.2615, left column), the limitation has been met by the teaching of Ling et al.

Although Lumelsky et al. do not particularly disclose that the proportion of pancreatic endocrine cells being at least 4 percent, since it is disclosed that more than about 50%, 80% or 90% of the cell culture being pancreatic stem cells (see paragraph [0100]), it would have been obvious to consider that pancreatic endocrine cells differentiated from the pancreatic stem cells being more than 4%.

With regard to the insulin secretion rate of at least 6 microunits of insulin per one hundred thousand cells per hour, this limitation is considered as a property of cells resulted from the method of the current application. The "wherein" clause in claim 200 merely states the result of the limitations in the claim, and therefore, adds nothing to the patentability or substance of the claim. Therefore, this phrase does not limit the claim. See *Texas Instruments Inc. v. International Trade Commission*, 26 USPQ2d 1010 (Fed. Cir. 1993); *Griffin v. Bertina*, 62 USPQ2d 1431 (Fed. Cir. 2002); *Amazon.com Inc. v. Barnesandnoble.com Inc.,* 57 USPQ2d 1747 (Fed. Cir. 2001). Nevertheless, the insulin producing cells of Lumelsky et al. are considered to have the same intended results as the claimed invention in the absence of evidence to the contrary.

Although Lumelsky et al. in view of Dang et al. in further view of Ling et al. do not

particularly teach trypsinization step of surface bound cell clusters (claim 205), as Ling et al. disclose a culture condition for single cell suspension culture for maintaining insulin producing cells, a person of ordinary skill in the art would dissociate insulin cell clusters of Lumelsky et al. to obtain single cell suspension for the method of Ling et al. Furthermore, since Lumelsky et al. teach trypsin for dissociation of insulin cell clusters (see paragraph [0176]), it would have been not only an inherent result of the trypsinization step of Lumelsky et al. to obtain dissociated single cells of the surface bound insulin cell clusters of Lumelsky et al., but a person of ordinary skill in the art would utilize trypsin for dissociating insulin cell clusters of Lumelsky et al. in order to obtain single cells for maintaining insulin producing cells by using the culture condition of Ling et al.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 193, 214 and 215 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lumelsky et al. (supra) in view of Dang et al. (supra) in further view of Thomson et al. (of record).

Lumelsky et al. in view of Dang et al. render the limitations of claim 193 and 214 obvious (see above).

Lumelsky et al. in view of Dang et al. do not teach the use of H13 cells.

Thomson et al. teach that H13 cell line is an embryonic stem cell line derived from human blastocysts (see whole document; p.1145, middle column; Fig. 2).

It would therefore have been obvious for the person of ordinary skill in the art at the time

the invention was made to replace the human ES cells of Lumelsky et al. with H13 cells of Thomson et al. in the method of Lumelsky et al. because a person of ordinary skill in the art would recognize the H13 cells of Thomson et al. would be art-acceptable equivalent to the human ES cells of Lumelsky et al.

M.P.E.P. §2144.06 states "In re Scott, 323 F.2d 1016, 139 USPQ 297 (CCPA 1963) (Claims were drawn to a hollow fiberglass shaft for archery and a process for the production thereof where the shaft differed from the prior art in the use of a paper tube as the core of the shaft as compared with the light wood or hardened foamed resin core of the prior art. The Board found the claimed invention would have been obvious, reasoning that the prior art foam core is the functional and mechanical equivalent of the claimed paper core. The court reversed, holding that components which are functionally or mechanically equivalent are not necessarily obvious in view of one another, and in this case, the use of a light wood or hardened foam resin core does not fairly suggest the use of a paper core.); Smith v. Hayashi, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.)."

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651